

## REMARKS

Applicants acknowledge and thank the Examiner for granting the telephone interview on September 10, 2008.

### IN THE CLAIMS

Claims 2, 4, 5, and 9 have been canceled. Claims 1, 6-8, 10, 11, 21, 22, and 24 have been amended for greater clarity and particularity, and to point out the subject matter regarded by Applicants as the subject of the invention.

Claims 1, 6, 7, 10, 21, 22, and 24 have been amended for greater clarity and particularity to specify that the subject disease for which the claim methods are prognostic is a gastric preneoplastic/neoplastic disease. Applicants respectfully submit that those amendments are supported at the least by previous Claim 5, now canceled, wherein “said preneoplastic/preneoplastic disease is selected from the group consisting of neoplastic/preneoplastic diseases of gastric mucosa, gallbladder, biliary ducts and ductal cells of duodenal glands.” Further particular support for those amendments can be found throughout the specification, at the least in the Summary of the Invention, particularly at page 5, lines 11-18; and in Examples 1-5, at pages 38-41, which provide a working example of determining prognostic significance of MN/CA IX expression in gastric cancer patients.

Independent Claims 1 and 24 have also been amended for greater clarity to specify that the “gastric preneoplastic/neoplastic tissue sample(s)” comprise neoplastic cells. Claims 7, 10 and 11 have been amended to be directed to methods using gastric tissue samples. Support for those amendments can be found as indicated above, and in the instant specification at the least at page 7, lines 11-13, which reads: “In a preferred embodiment, the disease is gastric cancer, and the sample is taken from the invasion front of the gastric cancer.”

Claims 6, 7 and 10 have been amended to delete the term “neoplastic” to point out with more clarity and particularity the subject matter regarded by the Applicants as their invention. The antecedent in Claim 1 for the term “disease” in Claims 6 and 7 is “preneoplastic/neoplastic disease,” and in accordance with the

explanations concerning the oncogenic process discussed in the interview with the Examiner (as pointed out in the above summary), Applicants consider in that context for the term “neoplastic” alone to introduce an element of lack of clarity and particularity.

Independent Claim 1 has also been amended to indicate that the “comparable gastric preoplastic/neoplastic tissue samples comprising neoplastic cells” are taken from “vertebrates [that] are of the same species as the subject vertebrate. . . .” Support for the phrase “wherein said vertebrates are of the same species as the subject vertebrate” can be found in the instant specification at least at page 23, lines 12-13, which read: “The quantified MN/CA9 gene expression product levels are compared with the average levels in comparable samples taken from comparable patients. . . .” [Emphasis added.]

Finally, Claims 1, 8, 10, 21 and 24 have been amended for greater clarity and particularity to specify that the “poorer prognosis” of the subject vertebrate that is determined according to the claimed methods is a “prognosis of shorter survival.” Support for those amendments are found at the least in Claim 9, now canceled, which read: “The method of claim 1, wherein a poorer prognosis is measured in terms of shortened survival, increased risk of recurrence of said preneoplastic/neoplastic disease, or in diminished or refractory response to treatment.” Further support for those amendments can be found in the instant specification at the least at page 9, lines 22-30; at page 21, lines 23-28 [figure legend for Figure 5]; at page 22, line 26 to page 23, line 1; at page 27, lines 26-30; at page 40, lines 7-17 [Example 3, “Prognostic significance of CA IX expression in gastric cancer”]; and in Figure 5.

Applicants respectfully submit that no new matter has been entered by the above amendments.

#### I. 35 USC 112, First Paragraph (Enablement)

Claims 1, 2, 4-11, 14, 16 and 18-24 stand rejected under 35 USC 112, first paragraph, for failing to comply with the enablement requirement [Office Action dated June 20, 2008 (“Instant Office Action”), at page 3.] The Examiner states that the claims lack enablement because the specification,

[w]hile being enabling for a method of predicting survival of a patient with gastric cancer . . . , does not reasonably provide enablement for a method which is prognostic for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, . . . , and (d) determining that said subject vertebrate has every type of poorer prognosis. . . .

[Instant Office Action, at page 3; emphasis in the original.] Applicants respectfully rely upon their earlier responses dated 8/16/07 (at pages 30-37) and 12/19/07 (at pages 19-27), and in their Request for Continued Examination (RCE) dated 3/26/08 (at pages 20-42). Applicants further respectfully submit that the amendments to the claims overcome the instant rejection, answering the Examiner's concerns regarding the subject disease, the subject tissue samples to be used, the prognosis that is determined according to the claimed methods, and the support provided by the working example. Both of the independent claims, Claims 1 and 24, have been amended to be directed to 1) prognostic methods for gastric preneoplastic/neoplastic diseases, comprising the use of 2) gastric preneoplastic/neoplastic tissue samples comprising neoplastic cells, and 3) determining that said subject vertebrate has a prognosis of shorter survival. Applicants will discuss in greater detail below how the claim amendments address each of the Examiner's concerns.

Applicants respectfully point out that said amendments are being made without prejudice, in the interest of expediting prosecution of the instant claims. Applicants respectfully reserve the right to file additional claims in a continuation application to protect the invention commensurate with the scope as originally filed.

#### Examiner's Statement of Allowable Subject Matter

In the instant Office Action and in the Office Action dated 10/19/07 (mistakenly referred to by the Examiner as "the Office Action of 10/19/08" in the instant Office Action), the Examiner indicates that the specification is

enabling for a method of predicting survival of a patient with gastric cancer comprising (a) detecting MN/CA IX

polypeptide in a sample comprising gastric cancer tissue, (b) quantitating the level of said MN/CA IX polypeptide in said sample, (c) comparing the level of MN/CA IX polypeptide of step (b) to the average level of MN/CA IX polypeptide in analogous samples from subjects with gastric cancer, (d) determining that said patient has a prognosis of shorter survival than the average subject with gastric cancer if the level of MN/CA IX polypeptide level of step (b) is higher than the average level of MN/CA IX polypeptide in analogous samples from subjects with gastric cancer. . . .”

[Instant Office Action, at page 3; emphasis added.] In view of that guidance provided by the Examiner, Applicants respectfully point out that the two independent claims, Claims 1 and 24, have been amended to be directed to methods which are prognostic for a gastric preneoplastic/neoplastic disease, comprising (a) detecting MN/CA IX protein or MN/CA IX polypeptide in a gastric preneoplastic/neoplastic tissue sample comprising neoplastic cells; (b) quantitating the level of said MN/CA IX protein or MN/CA IX polypeptide in said sample; (c) comparing the level of MN/CA IX protein or MN/CA IX polypeptide of step (b) to the average level of MN/CA IX protein or MN/CA IX polypeptide in comparable gastric preneoplastic/neoplastic tissue samples comprising neoplastic cells taken from vertebrates also afflicted by a gastric preneoplastic/neoplastic disease, wherein said vertebrates are of the same species as the subject vertebrate, and (d) determining that said subject vertebrate has a prognosis of shorter survival if the level of MN/CA IX protein or MN/CA IX polypeptide of step (b) is higher than the average level of MN/CA IX protein or MN/CA IX polypeptide in said comparable gastric tissue samples.

As discussed further below, Applicants respectfully submit that the claimed methods now specify the specific disease, types of tissue samples, and type of prognosis indicated by the Examiner as allowable subject matter in the instant Office Action. In addition, the Specification provides working examples for the use of MN/CA IX immunological assays for a gastric cancer prognosis of shorter survival [Examples 1-5]. As the amended claims now specify the specific disease, tissue, and type of prognosis for which the claimed methods apply, corresponding to subject matter previously indicated by the Examiner as allowable, the references cited by the Examiner as “evidence why the instant invention is not enabled in [sic] commensurate with the

scope of the claims” [Instant Office Action, at pages 15-17] no longer apply. Accordingly, Applicants respectfully submit that the claims should now be found allowable by the Examiner.

#### Scope of the Claims Limited

##### A. Subject Disease and Subject Tissue Samples

Beginning at page 10 of the instant Office Action, the Examiner states that [i]n the broadly claimed invention, undue experimentation would be required even with recitation of which tissues are to be used in the claimed invention. For instance, the claims are broadly drawn to a method which is prognostic for every preneoplastic/neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/C AIX expression upon carcinogenesis. . . . The nature of the invention is cancer prognosis based on expression of a particular biomarker that has not been shown to be prognostic as claimed for the diseases encompassed by the claims.

[Emphasis in the original.] Applicants respectfully point out that the independent claims (Claims 1 and 24) are now drawn solely to a prognostic method for “a gastric preneoplastic/neoplastic disease,” and the subject tissue sample used according to method step (a) is a “gastric preneoplastic/neoplastic tissue sample comprising neoplastic cells” (Claim 1) or a “gastric tissue sample comprising neoplastic cells from the invasion front of said [gastric] preneoplastic/neoplastic disease” (Claim 24).

##### B. Subject Comparable Tissue Samples

Then, the Examiner states at page 13 of the instant Office Action that “[i]n regards to the argument that ‘comparable samples’ are samples from a patient’s tumor/metastatic lesion and/or tissues adjacent thereto, Applicant is arguing limitations not recited in the claims or required by the disclosure. . . . [T]he claims encompass methods of using just any sample as a ‘comparable sample.’” Applicants respectfully point out that the original claims were, and the subject claims [see PCT/US 2004/034573 and WO 2005/037083] have always been directed to “comparable

samples.” The claims now as amended refer to “comparable gastric preneoplastic/neoplastic tissue samples comprising neoplastic cells” taken from patients that are also afflicted by a gastric preneoplastic/neoplastic disease. Applicants respectfully submit that the amended claims do not encompass methods of using just any sample as a “comparable sample,” and instead correspond in scope with methods using “analogous samples from subjects with gastric cancer” indicated as allowable by the Examiner [Instant Office Action, at page 3].

C. Type of Poorer Prognosis

Regarding the scope of “poorer prognosis” that could be determined using MN/CA IX, in response to Applicants’ previous evidence of the Cancer Imaging Program of the National Cancer Institute considering the use of MN/CA IX as a generalized biomarker of different types of poor prognosis, the Examiner maintains that “[e]ven in light of what is known in the art of MN/CA IX” [Instant Office Action, at page 15], it would require undue experimentation to enable the claimed methods for determining multiple types of poorer prognosis, that is, other prognoses than the prognosis of shorter survival found in the Examples. Applicants respectfully point out that independent Claims 1 and 24 have been amended, such that the instant claims are now drawn to methods which determine a prognosis of shorter survival for gastric preneoplastic/neoplastic disease, rather than to multiple types of cancer prognosis.

D. Working Example

Beginning at the bottom of page 11 of the instant Office Action, the Examiner states that “[w]hile Applicant provides a single working example of the claimed invention, said working example does not demonstrate the invention would predictably function as broadly claimed based on the unpredictability of the art and what is known in the art.” Although (as confirmed by the Examiner at page 12 of the instant Office Action) Applicants do not have to present working examples before filing to meet the enablement requirement, Applicants respectfully point out that the working examples provided in the instant specification in Examples 1-5 specifically support the

methods of the amended claims, relating to a prognosis of shorter survival in patients with gastric cancer.

At the bottom of page 4 of the instant Office Action, the Examiner repeats his comments from the Office Action of 5/17/07, indicating that in particular Example 2, Example 3, and Figure 5 of the instant specification support “a method which is prognostic for a patient with gastric cancer.” Therefore, Applicants respectfully submit that there should be no question of enablement for the claimed methods.

E. Cited References

At page 14, the Examiner refers to the previously cited Tockman et al. article, stating that

Tockman et al is cited as a teaching that demonstrates that unpredictable state of the art and the state of the art for determining whether a particular biomarker is indicative of a particular disease state. . . . A particular prognosis is a disease end point that is obviously amenable to the methods taught by Tockman et al.

Applicants respectfully point out that the instant claims as amended are directed to the use of MN/CA IX for determination of a particular prognosis, shorter survival, in gastric cancer patients, for which working examples are provided in the instant specification, and therefore, Tockman et al. support the enablement of the claimed methods.

In addition, the Examiner cites four references at pages 15-17 of the instant Office Action [Matsumura et al., Neurol Med Chir, 37: 916-919 (1997); Hicks et al., Urol Int, 70(3): 247-8 (2003); Young et al., Int J Gynecol Pathol, 11(2): 96-104 (1992); Ishizawa et al., Asian J Surgery, 29(3): 145-148 (2006)], as evidence of renal cell carcinoma metastasizing to tissues previously encompassed by the claims (gallbladder, ovary, testis, or central nervous system choroids plexus tissues; i.e., “said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses . . . expression upon carcinogenesis,” recited in previous Claim 1), and consequently evidence of inoperative embodiments of the claims as previously written (as a lower than average level of MN/CA IX indicates a poorer prognosis in renal cell carcinoma).

Applicants respectfully point out that those four latter references are now irrelevant to the claims as amended, as the subject disease recited in the claimed methods is now unambiguously specified to be a gastric disease, and the subject and comparable tissue samples to be gastric tissue samples. Therefore, Applicants respectfully submit that the Examiner's concerns have been met regarding the successful practice of the claimed invention commensurate with the scope of the claims.

#### Enablement Conclusion

In view of the amendments to the claims and the above remarks, Applicants respectfully conclude that the claims as amended align with the subject matter which according to the Examiner's Statements are sufficiently supported to meet the enablement requirement, and respectfully request that the Examiner withdraw the instant 35 USC § 112, first paragraph enablement rejection.

#### CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Agent for Applicants at (415) 981-2034.

Respectfully submitted,

A handwritten signature in cursive script, reading "Joan C. Harland".

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